Effect of lead design and pacing vector on electrical parameters of quadripolar coronary sinus leads: The RALLY-X4 study

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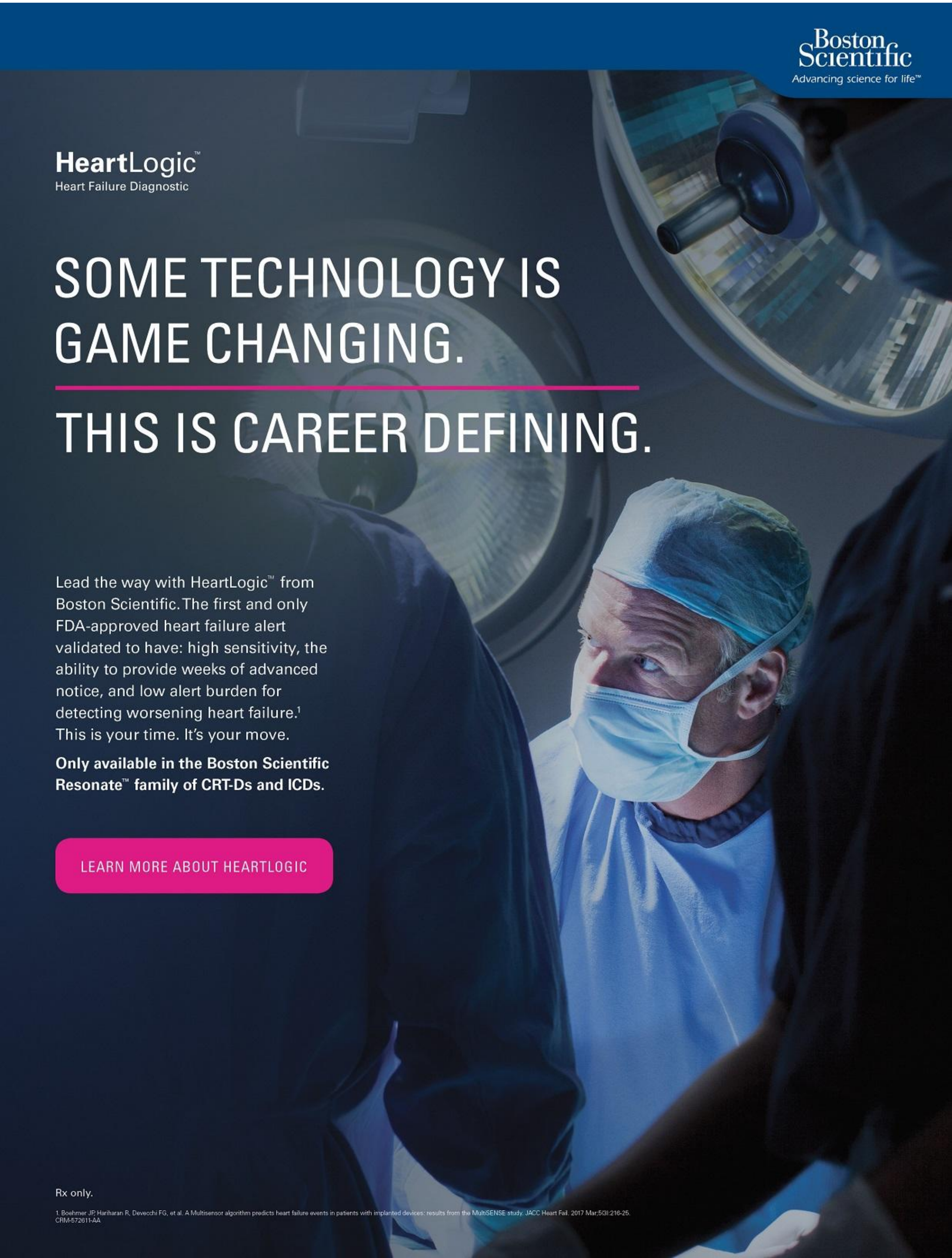
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Effect of lead design and pacing vector on electrical parameters of quadripolar coronary sinus leads: the RALLY-X4 study

Short title: Lead design and electrical parameters

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ABSTRACT

Background: Various lead designs have been developed to accommodate different coronary sinus anatomies. Our objectives were to compare electrical parameters of straight and spiral left ventricular leads, to evaluate capture thresholds and impedances using different pacing vectors, and to study evolution of thresholds over time.

Methods: The RALLY-X4 study enrolled patients implanted with a lead from the Acuity X4 family (Straight, Spiral Short or Spiral Long). Electrical parameters (including capture thresholds from all 17 vectors) were measured at baseline and follow-up.

Results: Data from 795 patients who were successfully implanted were analysed. Straight and spiral leads had similar proportions of patients with thresholds <2.5V/0.4ms using the distal electrode (61-65% of patients) or from at least one of the proximal (E2-E4) electrodes (81-83% of patients). Unipolar vectors had significantly lower thresholds and impedances than bipolar vectors, with similar measurements compared to extended bipolar configurations. Capture thresholds increased with more proximal electrodes for all leads. Over a mean follow-up of one year, a slight decrease in capture thresholds was observed.

Conclusion: Straight and spiral quadripolar leads allow to obtain clinically acceptable capture thresholds from at least one of the proximal electrodes in >80% of patients. Pacing vectors significantly affect electrical parameters, with higher thresholds in more proximal electrodes and lower thresholds with unipolar and extended bipolar configurations. Capture thresholds slightly decreased over a mean follow-up of one year.

Keywords: Cardiac resynchronization therapy; pacing leads; capture threshold; impedance.

INTRODUCTION

The most important aspects of left ventricular (LV) lead position for cardiac resynchronization therapy (CRT) are hemodynamic effect, stability, and adequate electrical parameters. Quadripolar LV leads have had a significant impact in this therapy by providing more programming options to maximize CRT delivery. A meta-analysis of eight studies (1) and a report with a large real-world experience (2) have shown that quadripolar leads have lower rates of implantation failure, post-operative lead dislodgement, revision or deactivation. Clinical outcome in terms of mortality and heart failure hospitalization have also been shown to be reduced with quadripolar leads compared to bipolar leads in a non-randomized but matched population.(3) Manufacturers propose quadripolar leads of different diameters, shapes and interlead spacing to address variations in coronary sinus (CS) tributary anatomy. Boston Scientific (Marlborough, MA) offer the ACUITY X4 lead family which are either of a straight or a spiral shape, with 17 different programmable vectors - (see figure 1). The performance of this lead family has been previously described.(4; 5) In the NAVIGATE X4 study,(5) there was an overall LV-lead 6-month complication-free rate of 98% in 791 patients. However, not all pacing vectors were tested in this study, and follow-up was limited to 6 months without reporting evolution of thresholds.

The RALLY-X4 study is a post-market surveillance registry for Acuity X4 leads, where investigators were encouraged to report electrical parameters for all 17 vectors at each follow-up. This provided us with the opportunity to study in detail different pacing vectors in a large dataset. Our aims were to compare1) electrical measurements of straight and spiral leads 2) capture thresholds and pacing impedances of different pacing polarities and 3) to study evolution of capture thresholds over time for straight and spiral leads.

METHODS

Study design

The RALLY-X4 study was a non-randomized, unblinded, multicentre observational study conducted in 82 centres in Europe, Japan, Singapore, Hong Kong and Colombia. All patients were implanted with a biventricular defibrillator (CRT-D) and an Acuity X4 lead (the lead model was left to the discretion of the investigator). Implant procedure and subsequent follow ups were based on hospital standards. The study collected patient indication and demographics, all adverse events, and selected programming data.

LV Capture thresholds were measured at 0.4ms, and investigators were encouraged to report electrical measurements for each of the 17 programmable vectors at baseline and at close out visits. In order to account for electrodes with non-capture, which are not taken into account when calculating median thresholds, we evaluated the proportion of electrodes for each lead with capture thresholds (in any configuration) at baseline based upon an arbitrary cutoff of 2.5/0.4ms (as previously reported(5; 6)). Blank fields were assumed to be non-capture and counted as thresholds

>2.5V. Evolution of thresholds was evaluated by paired measurements of the unipolar vector for each electrode at baseline and the closeout visits.

Occurrence of phrenic nerve stimulation (PNS) and any loss of function of the LV lead or requirement for lead repositioning were reported and counted toward the study endpoint. Final lead position (based on the lead tip), baseline and close out ECGs were assessed by corelabs based upon uploaded files, fluoroscopic or X-ray images. The study was approved by the institutional ethics committees, and all patients provided written informed consent.

Statistical analysis

Analysis was performed using the SAS 9.4 software (Cary, USA). Descriptive statistics report values as mean±SD or median±interquartile range, as appropriate. Differences between groups were evaluated using the Chi-squared and Kruskal-Wallis test. Changes in electrical parameters over time were evaluated for each cathode by paired analyses at baseline and at last follow-up using the Wilcoxon signed rank test. A P value of <0.05 was considered statistically significant.

RESULTS

Patient population

Of the 863 patients enrolled, 838 underwent a procedure and 795 patients (94.9%) were successfully implanted with an Acuty X4 lead (one patient at the second attempt). Patient demographics are shown in table 1. A total of 147 patients discontinued the study, of whom 54 died. Mean follow-up was 12.8 ± 5.9 months.

General findings

Spiral leads were more often placed in an apical position than straight leads, without any differences in anterior versus non-anterior lead position (table 2). Of the 155 patients evaluated by the corelab as having the lead tip in an apical position, 143 had sufficient electrical data for analysis. Of these, 113 (79%) had E3 and/or E4 with a capture threshold of <2.5V/0.4ms.

A PNS-related adverse event was reported in 49 (5.8%) patients at six months follow-up, of whom lead revision was required in four (0.5%) patients with no additional cases between the six and 12-month timepoints. Details on PNS with different pacing configurations were available in 726 patients. PNS in at lead one configuration for Straight, Spiral Short and Spiral Long leads were reported in 10.9%, 3.7% and 5.9% of cases respectively. PNS was associated with E1 (4.7%), E2 (4.6%), E3 (2.6%) and E4 (10.7%). Polarities associated with PNS were unipolar (10.3%), extended bipolar (4.8%) and bipolar (2.7%). Pectoral muscle stimulation was not reported in any patient programmed to a unipolar pacing configuration.

There were a total of 6 (0.8%) lead dislodgements over the course of the study, of whom four patients underwent revision, one lead explantation and one lead inactivation.

At the programmed vectors for LV pacing and sensing at baseline and closeout visits for each lead model, the median values for capture thresholds were 1.0-1.3V, for pacing impedance, 683-736 Ohms and for sensing amplitudes, 13.9-17.0mV.

Comparison of electrical parameters between leads

The results of electrical parameters in 795 patients at baseline are shown in table 3. Data fields for thresholds measurements of the 17 possible vectors in each patient were left blank in 21.7% of fields and were assumed to be non-capture.

In order to analyse separately distal E1 electrodes which are often implanted in an apical position and the proximal E2-4 electrodes (which are most often used to avoid apical pacing associated with reduced response to CRT(7; 8)), we performed an analysis comparing the numbers of proximal electrodes which offered thresholds <2.5V (see figure 2). The proportions of patients with Straight, Spiral Short and Spiral Long leads with E1 thresholds <2.5V were 65%, 64% and 61% respectively; the same analysis for at least one proximal electrode (E2-4) were 81%, 83% and 83% respectively (P=NS). The Straight lead had a significantly greater proportion of patients with two or all three proximal electrodes with low thresholds: 59% versus 48% for Spiral Short (P=0.013) and 39% for Spiral Long (P<0.0001). There were no differences between spiral leads.

Effect of pacing vector on capture thresholds and lead impedance

As shown in table 3, pacing vectors had a highly significant impact on capture threshold and lead impedance for all four electrodes of all three leads. Unipolar and extended bipolar configurations (see figure 1) had in general lower capture thresholds than true bipolar configurations, except for the E4 electrode of spiral leads. In general, extended bipolar configurations had similar thresholds compared to unipolar vectors. Different bipolar pacing vectors for a given cathode (e.g. E1-E2, E1-E3 and E1-E4) had no significant impact on thresholds for any electrode of any lead.

The E1 and E2 electrodes usually had greatest (and similar) proportions of low thresholds, whereas the proportion of low thresholds decreased with E3 and E4 electrodes. Regarding impedances, unipolar vectors were approximately 50-60% of those for bipolar vectors (P<0.001 for all comparisons) and approximately 90% of extended bipolar vectors (P<0.05 for all comparisons).

Evolution of capture thresholds and pacing impedances over time

The data are displayed in figure 3. Overall, we observed a slight reduction in capture thresholds, a slight decrease in E1 pacing impedance and a slight increase in pacing impedance of the E2-4 electrodes. An approximation of the current drain was calculated by I=V/R, although the actual value would result from the programmed output voltage, and not the threshold voltage.

DISCUSSION

The main findings of our study are that 1) Straight and Spiral leads perform well with high implant success and low dislodgment rates at one-year follow up 2) Capture thresholds of <2.5V/0.4ms are obtained from at least one proximal electrode (E2-4) in >80% of cases 3) Unipolar and extended bipolar vectors yield significantly lower thresholds and impedances compared to bipolar configurations 4) Capture thresholds most often show a slight decrease over follow-up with all lead types.

A proximal (E2-4) electrode was used as a cathode in the majority of patients in our study (63-74% depending on the lead model), most probably in order to avoid pacing from an apical site (where lead tips are often wedged for stability), as is currently recommended.(9) The NAVIGATE X4 study showed that proximal electrode thresholds were lower with spiral leads compared to straight leads.(5) Overall, 91% patients implanted with a spiral lead had a threshold <2.5 V from a "best-proximal" electrode (median 0.9 V [IQR 0.7, 1.3]). The same analysis for the straight leads yielded a proportion of 83% (P=0.003) with higher absolute thresholds (median 1.3 V [IQR 0.9, 2.2]). This is in contrast with our findings which show that all three lead types had a similar proportion of patients (81-83%) with at least one proximal electrode with a threshold <2.5V, and in fact a higher proportion of patients with at least two or all three proximal electrodes with low thresholds in patients with straight leads. Differences in findings with the NAVIGATE X4 study may be possibly explained by the fact that all 17 pacing vectors were evaluated for our analysis, whereas this was not the case for NAVIGATE X4. In fact, a significantly higher proportion of patients with straight leads than spiral leads had at least two or all three proximal electrodes with thresholds <2.5V. The spiral design of the leads probably resulted in fewer proximal electrodes having good myocardial contact, which explains this finding. An additional finding was that E3 and E4 electrodes had higher thresholds, and this was consistent for all lead models. Interestingly, the same findings were reported in leads with different designs from other manufacturers,(6; 10; 11) and possibly stem from less intimate contact with the myocardium of these electrodes. Capture thresholds are also likely to be affected by the anatomy of the coronary sinus tributary (vessel diameter, tortuosity etc). Not surprisingly, we found that lead models were positioned differently e.g. Spiral leads were more often in an apical position (and probably in larger veins) than Straight leads. This is an important confounding factor which needs to be accounted for when comparing performance of different lead models.

In agreement with our findings, previous studies using leads from other manufacturers have reported that extended bipolar pacing vectors yield lower capture thresholds than bipolar configurations.(6; 10) For the first time, we also report unipolar vectors (currently only available on CRT-Ds of Boston Scientific) and found them to be comparable to extended bipolar vectors. The advantage of unipolar pacing is avoidance of anodal capture (which, although less likely with the RV coil of and ICD lead than with the ring of a pacing lead, is still possible(12)). This may be an issue if sequential biventricular pacing with left ventricular pre-excitation is desired, or in case of device follow-up with non-identification of LV lead dislodgment. However, the tradeoff with unipolar and extended bipolar vectors compared to bipolar configurations is a lower pacing impedance (which was also reported in the NAVIGATE-X4 study(5)), as this leads to higher current drain. Another possible drawback in case of high pacing output in the unipolar configuration is pectoral muscle capture. The most frequently programmed vectors in our study were extended bipolar for all three leads.

Comparison of electrical performance between Acuity X4 leads and quadripolar leads of other manufacturers is difficult, owing to differences in reporting of data e.g. capture thresholds measured at 0.5ms pulsewidth and expressed as mean±SD in these reports (6; 10) compared to 0.4ms and median±interquartile range in our study.

Along with the study by Lin et al,(11) our study provides the longest available follow-up data of electrical parameters for LV leads, with an average follow-up of one year. Overall, there was a slight reduction in capture thresholds at follow-up, which was more marked for the two most proximal electrodes of spiral leads. Pacing impedance for E1 fell slightly for all three lead models, while the impedances of the proximal electrodes slightly increased. These observations may be due to the iridium oxide coating of the electrodes, better tissue contact of the electrodes with time, and/or to tributary vein thrombosis and stabilisation of the lead.

Study limitations: Blank data fields for threshold measurements (present in 21.7% of fields) were assumed to be non-capture (i.e. reported as >2.5V/0.4ms), which is very likely to have yielded a conservative analysis of overall lead performance. However, potential omissions in data reporting are likely to have involved the three lead models to a similar extent, without unduly affecting their comparison. Pulse widths may have been increased by investigators during the duration of the study in case of elevated thresholds; threshold tests may have not been performed at 0.4ms pulsewidth as stipulated in the protocol, which may have accounted for the observed decrease in threshold amplitude over follow-up. PNS was reported according to clinical observation, and not sought after systematically and may therefore have been underreported. However, adverse events resulting from PNS (e.g. requirement for reprogramming or reintervention) were captured, and we therefore believe that most clinically-relevant cases have been reported in our study.

CONCLUSION

Various lead designs have been developed to accommodate for different coronary sinus anatomies. Basal and mid-ventricular pacing sites are usually desirable, but capture thresholds increase with more proximal electrodes of quadripolar leads. Nevertheless, straight and spiral leads provide thresholds of <2.5V/0,4ms in at least one of the proximal electrodes in >80% of cases, with lower thresholds in unipolar and extended bipolar configurations, which slightly decrease over follow-up.

Author contributions:

H.B., T.K. and M.B. participated in the concept and design of the study. H.B. interpretation the data, and drafted the article. T.K. provided the statistical analysis. All authors critically revised and approved the article.

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Figure legends

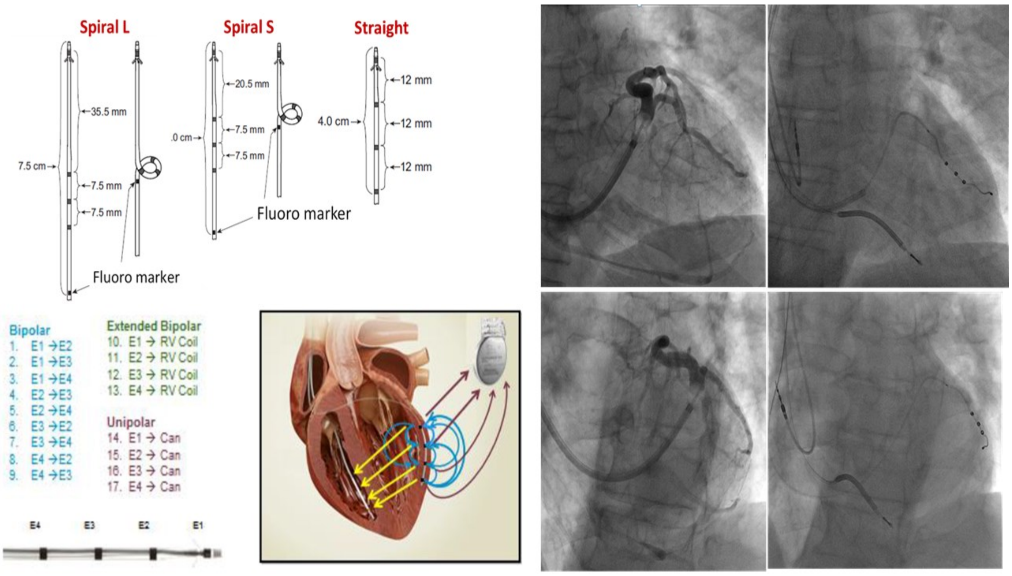

Figure 1: Acuity Spiral long (L), Spiral Short (S) and Straight lead models, with the 17 programmable pacing vectors (including unipolar pacing for CRT-Ds). Spacing between the distal (E1) and most proximal (E4) electrode is comparable between the Acuity Straight and Spiral S leads, and is similar

to spacing between E1-E2 of the Spiral L lead. All leads have a steroid-eluting collar drug collar near the tip which is separate from the iridium-oxide coated electrodes. On the right, postero-anterior (top) and left anterior oblique (bottom) views of a coronary sinus angiogram are shown, along with final lead position of a Spiral L lead in an apical position of a large lateral tributary (note the proximal fluoroscopic marker which is well within the branch). By virtue of the large spacing of the Sprial L lead, the three proximal electrodes are in a mid-ventricular position.

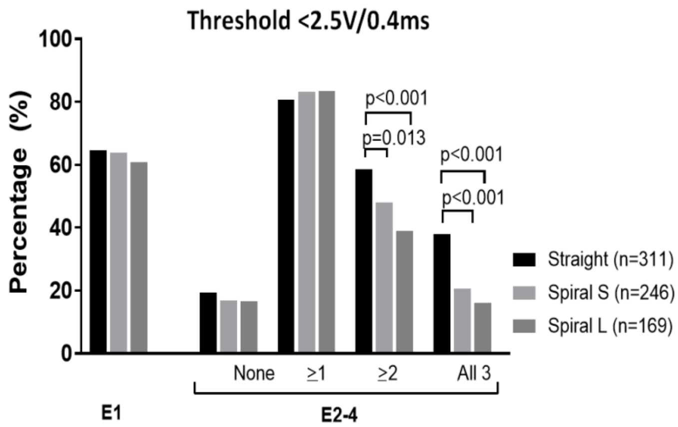

Figure 2: Comparison between lead models for proportion of low capture thresholds (<2.5V in any polarity) for distal (E1) and proximal (E2-4) electrodes at baseline for Straight, Spiral Short (S) and Spiral Long (L) leads at baseline. Blank data fields (representing 21.7% of data) were assumed to be non-capture and reported as >2.5V/0.4ms.

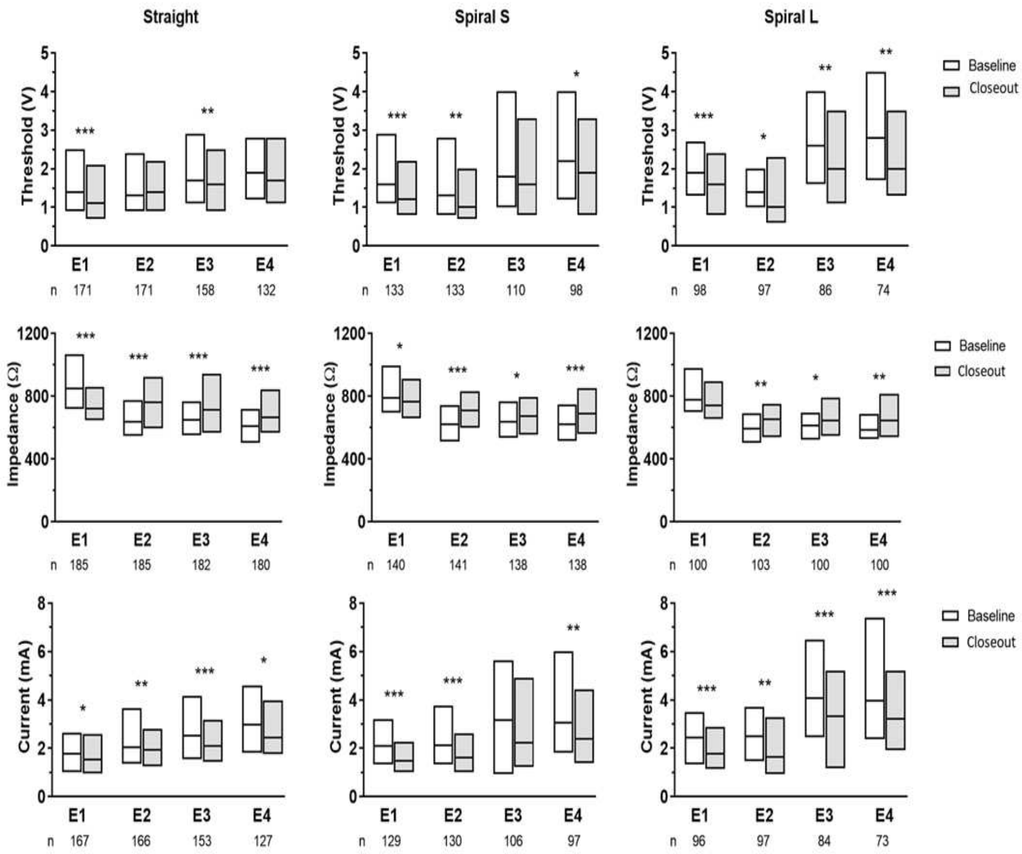

Figure 3. Evolution of unipolar capture thresholds (top) and lead impedances (middle) and approximated current drain calculated by threshold V/R (bottom) at baseline and closeout visits for the different electrodes (actual current drain would depend on programmed output voltage). Data displayed are median and 25th-75th percentiles. Paired values are shown for each electrode. Not all patients with impedance measurements had capture thresholds reported (e.g. because of lack of capture).*** P<0.001, ** P<0.01, * P<0.05).

Table 1. Baseline characteristics of patients who underwent implantation

	Enrolled subjects n= 838
Age (Years)	67.4 ± 10.1
Males	650 (77.6)
Ischemic cardiopathy	390 (46.5)
Rhythm disease history	
AV block	217 (25.9)

	Enrolled subjects n= 838
Chronic atrial fibrillation	158 (18.9)
Paroxysmal atrial fibrillation	139 (16.6)
Hypertension	521 (63.3)
Diabetes mellitus	283 (33.8)
Renal disease	191 (22.8)
Chronic pulmonary disease	92 (11.0)
Peripheral artery disease	48 (5.7)
Cardiac rhythm	
Sinus rhythm	512 (61.1)
Atrial fibrillation	174 (20.8)
Paced ventricular	99 (11.8)
Other	53 (6.3)
QRS morphology	
Normal	71 (8.5)
RBBB	76 (9.1)
LBBB	578 (69.0)
NIVCD	95 (11.3)
Pacemaker dependant or unknown	18 (2.1)
Intrinsic QRS width (ms)	158.1 ± 31.2
Intrinsic PR interval (ms)	187.9 ± 51.8
BMI (kg/m^2)	27.1 ± 5.0

Percentages are shown in brackets. AV= atrioventricular; BMI=body mass index; LBBB=left bundle branch block; ms=milliseconds; NIVCD=non-specific intraventricular conduction delay; RBBB= right bundle branch block

Table 2. Lead positions for the different models (according to the distal E1 electrode position).

Numbers of datasets are limited to those provided by corelab analysis.

Lead model	Apical	Mid	Basal	Non Anterior	Anterior
Straight (N= 195) (4671 or 4672)	43 (22.1%)	127 (65.1 %)	25 (2.8 %)	189 (96.9%)	6 (3.1%)
Spiral Short (N= 170) (4674 or 4675)	54*# (31.8%)	106 (62.4%)	10*# (5.9%)	165 (97.1%	5 (2.9%)

Spiral Long (N= 121) (4677 or 4678)	53** (43.8%)	67 (55.3%)	1** (0.8%)	120 (99.2%)	1 (0.8%)

** P<0.001 compared to Straight lead; * P<0.05 compared to Straight lead; # P<0.05 compared to Spiral long lead.

Table 3. Lead data at baseline (implantation/predischarge). Blank data fields (representing 21.7% of data) were assumed to be non-capture and reported as >2.5V/0.4ms.

Vector	**Straight (n=325)**				**Spiral Short (n=288)**				**Spiral Long (n=182)**			
	Progr. vector	Threshold < 2.5V	Threshold	Impedance	Progr. vector	Threshold < 2.5V	Threshold	Impedance	Progr. vector	Threshold < 2.5V	Threshold	Impedance
E1 cathode	36.7 %				31.7 %				25.9 %			
Unipolar E1->Can	5.9 %	68.1%	1.5 [1.0-2.8]	858 [740-1034]	6.9 %	54.5%	1.9V [1.2-2.8]	834 [740-1034]	4.0 %	56.6%	2.0 [1.2-3.0]	815 [710-1034]
Ext. Bipolar E1->RV Coil	21.5 %	55.4%	1.5 [0.9-2.7]	966** [804-1156]	16.3 %	57.3%	1.8V [1.0-2.7]	902* [705-1000]	12.1 %	56.0%	2.0 [1.2-2.8]	973** [823-1178]
Bipolar E1->E2	8.3 %	52.9%	2.1** [1.4-3.5]	1340** [1132-1628]	6.1 %	43.8%	2.5 [1.7-4.0]	1339** [1142-1606]	6.9 %	42.9%	2.6** [1.7-3.8]	1331** [1118-1594]
Bipolar E1->E3	0	42.8%	2.4** [1.5-4.0]	1468** [1195-1755]	1.6 %	34.7%	2.8 [1.8-4.0]	1430** [1232-1640]	0.6 %	34.6%	2.8** [1.9-3.5]	1517** [1195-1718]
Bipolar E1-	1.0 %	44.8%	2.3** [1.5-	1441** [1176-	0.8 %	34.4%	2.8 [1.8-	1414** [1237-	2.3 %	34.1%	2.8** [1.8-	1472** [1216-

>E4			3.5]	1695]			4.0]	1675]			4.0]	1671]
E2 cathode	32.7 %				40.7 %				46.9 %			
Unipolar E2->Can	5.9 %	69.2%	1.5 [0.9-2.4]	628 [534-767]	6.9 %	59.0%	1.3 [0.8-2.6]	627 [524-750]	5.8 %	63.2%	1.4 [1.0-2.5]	594 [518-706]
Ext Bipolar E2->RV Coil	20.5 %	61.5%	1.2# [0.8-2.3]	701** [599-826]	21.6 %	62.2%	1.3 [0.7-2.4]	649# [569-784]	29.5 %	62.1%	1.3 [0.9-2.4]	652** [590-752]
Bipolar E2->E3	4.3 %	49.5%	2.3** [1.5-3.4]	1138** [966-1336]	9.8 %	52.8%	2.0** [1.3-3.3]	1052 [909-1306]	8.7 %	50.6%	2.1** [1.6-3.4]	1013** [836-1147]
Bipolar E2->E4	2.0 %	48.3%	2.3 [1.5-3.3]	1128** [963-1319]	2.4 %	52.1%	2.0** [1.3-3.3]	1094 [926-1327]	2.9 %	50.6%	2.2** [1.5-3.5]	1034** [874-1176]
E3 cathode	17.5 %				13.8 %				22.5 %			
Unipolar E3->Can	4.6 %	54.2%	1.8 [1.1-3.0]	647 [549-765]	2.0 %	41.0%	2.1 [1.1-4.0]	643 [543-768]	1.7 %	37.9%	2.6 [1.5-4.5]	617 [524-718]
Ext. Bipolar E3->RV Coil	8.9 %	51.1%	1.8 [1.0-2.7]	691** [595-828]	6.9 %	42.7%	2.1 1.1-3.6]	673# [581-793]	9.2 %	40.7%	2.3 [1.2-3.5]	673** [594-776]
Bipolar E3->E2	1.7 %	33.2%	2.7** [1.8-4.0]	1176** [978-1356]	2.0 %	31.2%	2.8** [1.7-4.5]	1098** [941-1346]	3.5 %	29.7%	2.9* [2.0-4.5]	1082** [926-1271]
Bipolar E3->E4	2.3 %	38.5%	2.5** [1.7-	1096** [902-	2.9 %	31.6%	2.8** [1.8-	1058** [902-	1.2 %	27.5%	3.0* [2.1-	1005** [830-

			4.0]	1289]			4.5]	1271]			5.0]	1005]
E4 cathode	13.2 %				13.5 %				11.6 %			
Unipolar E4->Can	5.3 %	46.2%	2.1 [1.3-3.2]	603 [502-721]	2.9 %	30.0%	2.6 [1.4-4.5]	634 [523-747]	2.3 %	27,5%	3.3 [1.9-5.0]	587 [521-692]
Ext Bipolar E4->RV Coil	5.9 %	41.2%	2.0 [1.2-3.3]	650** [571-792]	6.9 %	30.6%	2.6 [1.5-4.0]	654** [556-784]	7.5 %	29.7%	2.7 [1.6-4.5]	635* [565-732]
Bipolar E4->E2	0.7 %	22.5%	3.1** [1.9-4.5]	1290** [1069-1491]	0.8 %	21.2%	3.2 [1.9-4.5]	1180** [1026-1406]	0.6 %	19.2%	3.3 [2.1-4.5]	1186** [1054-1327]
Bipolar E4->E3	1.3 %	23.1%	3.0** [2.0-4.0]	1210** [1026-1471]	2.9 %	20.5%	3.2** [1.8-5.0]	1144** [991-1373]	1.2 %	20.3%	3.3 [2.2-5.0]	1132** [989-1297]

Values are shown as median and 25th-75th percentiles. # P<0.05; * P<0.01; ** P<0.001 compared to the unipolar configuration for the electrode acting as cathode. Thresholds reported at 0.4ms pulsewidth.